Major Kidney Clinical Research Studies and Projects Inventory*

Chronic Renal Insufficiency Cohort (CRIC) Study

1. Administrative Data

(a) Name of study/research project and acronym:

Chronic Renal Insufficiency Cohort (CRIC) Study.

(b) Type of study/research project (randomized clinical trial, epidemiological study, database, etc.):

The CRIC Study is an epidemiological study.

(c) Funding status (currently funded, study/project completed):

This study is currently funded through June, 2009.

(d) Recruitment status (recruitment completed, currently recruiting):

Recruitment is expected to begin in the spring of 2003.

(e) For studies/project currently recruiting: indicate total sample size/ number currently enrolled, anticipated period of recruitment:

The desired cohort size is 3,000 participants. Participants will be recruited over 33 months, beginning in the spring of 2003.

(f) Data coordinating center principal investigator contact information (mailing address, phone, fax, e-mail address):

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(g) Number of recruiting sites, list of principal investigators at recruiting sites, and contact information as in (f) above:

Seven clinical centers will recruit participants. Contact information for clinical center principal investigators is in Appendix A.

(h) List of principal investigators at central laboratories/facilities (identify type of central facility) and contact information as in (f) and (g) above:

Contact information for principal investigators at central laboratories and facilities is in Appendix B.

(i) Roster of Data and Safety Monitoring Board/Scientific Advisory Committee or other oversight committee(s):

The Scientific Advisory Committee roster is in Appendix C.

(j) Private-sector support (type of support, e.g., financial, donation of drugs/placebo, etc.):

Currently, there is no private sector support of the CRIC Study, although industry partnerships are currently under active discussion.

2. Study Design

(a) Objective:

The overarching aim of the Chronic Renal Insufficiency Cohort (CRIC) Study is to establish an enduring, collaborative CRI research group capable of examining hypotheses concerning disease etiology, diagnosis, health outcomes, and health services utilization among a cohort of patients with CRI.

(b) Study design:

The CRIC Study will enroll people across the spectrum of severity of renal disease to assure that a sufficient number of patients reach the primary study endpoints. Cohort members will be followed throughout the entire duration of clinical follow-up or until death. We expect that a minority of patients, up to 15%-30% based on the experience of the AASK study, will develop end stage renal disease (ESRD) during the study; once this occurs relevant modifications to their continuing follow-up evaluations will be implemented because risk factors that occur prior to ESRD may be very important for the risk of cardiovascular events occurring after ESRD treatment begins.

(c) Major inclusion criteria:

CRIC Study Sample Characteristics

Age Stratum	Eligible Estimated GFR Range (ml/min/1.73 m^2)	No Diabetes	Diabetes
21-44 years	20-70	12.5%	12.5%
45-64 years	20-60	25.0%	25.0%
65-74 years	20-50	12.5%	12.5%

(d) Major exclusion criteria

CRIC Study Exclusion Criteria

General Exclusion Criteria	
Institutionalized (e.g., prisoner, nursing home resident, skilled nursing facility resident)	Previously received dialysis (peritoneal and/or hemodialysis) lasting more than one month, based on patient self-report
Unable or unwilling to provide informed consent	Prior organ or bone marrow or renal transplant, based on patient self-report
Life expectancy less than three years as judged by the subject's primary physician, based on site investigator's assessment	Received immunosuppressive or other immunotherapy for renal disease within the past six months before enrollment, based on patient self-report
NYHA Class III or IV heart failure at baseline	Received chemotherapy or alkylating agents for systemic cancer other than non-melanoma skin cancer within 2 years prior to enrollment, based on patient self- report
Received treatment for systemic vasculitis that affects the kidneys (e.g., anti-GBM, ANCA, lupus, etc.)	Previous diagnosis of myeloma
Known cirrhosis, based on patient self-report	Previously diagnosed polycystic kidney disease based on patient self report
Known HIV infection and/or AIDS, based on patient self-report	Currently participating in an interventional clinical trial (i.e., primarily trials of therapeutic agents that may have an effect on renal or cardiovascular outcomes as assessed by a Central Adjudication Committee)
Present participation in the AASK Cohort Study	
Additional Exclusion Criteria for Participants Undergoing ^{125}I-Iothalamate GFR Testing	
Known iodine allergy	Currently breast feeding, or pregnant based on urine HCG test
Impaired urinary voiding	Radiation exposure to γ-emitting isotope other than technetium

(e) Description of the intervention(s):

This is an observational study, there is no intervention component.

(f) Baseline/eligibility visit schedule (number of visits, major assessments):

CRIC study participants will be followed for up to six years, depending on the date of enrollment. A pre-screening telephone contact will determine if someone is potentially eligible to participate. If interested, participants will be scheduled for a *screening visit* during which the following will occur:

- Informed consent process; consent obtained
- Eligibility assessment questionnaire
- Contact information provided
- Demographic information collected
- Blood draw (10 cc) for serum creatinine (to calculate eGFR and determine eligibility), cystatin C and glucose
- Urine dipstick test for presence of glucose

This visit will take approximately 1 to 1.5 hours. Instructions and supplies will be provided for the collection of a 24 hour urine sample for use in the event the eGFR calculation identifies the potential participant as eligible. Patients will be instructed to complete a food frequency questionnaire that asks detailed information about the food they eat. If eligible, participants will return to the baseline visit with this questionnaire completed.

If a person is eligible according to the information collected during the screening visit, she or he will be scheduled within 30 to 45 days for a *baseline visit*. This visit is considered study enrollment, during which the following will occur:

- Eligibility assessment confirmed
- Detailed medical history obtained
- Fasting blood draw (100 cc) for the following tests (if consent to obtain a research sample for genetic studies was obtained, this blood draw will be used to store this sample):

  -CBC [hemoglobin, hematocrit, WBC, MCV, MCHC, platelets]

-Metabolic panel [albumin, total bilirubin, calcium, carbon dioxide, chloride, creatinine, glucose, alkaline phosphatase, potassium, total protein, sodium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), magnesium, phosphorus, total cholesterol, triglycerides, urea nitrogen]

-Cystatin C, HbA1C, homocysteine, troponin I, PTH and fibrinogen

- Urine assay for creatinine, protein, albumin, urea nitrogen
- Concomitant medication information
- ECG
- Ankle-brachial index
- Anthropometric measures (height, weight, mid-abdominal circumference, hip circumference)
- Assessment questionnaires of nutrition, physical activity, quality of life, depression, cognitive function, and health resource utilization
- GFR test (if selected for this sub-cohort)

This visit will take approximately two to three hours and will occur annually. Participants selected for the study will spend an additional three to four hours at this visit. The GFR test will be repeated two and four years after enrollment. One year and four years after enrollment, all participants will also be scheduled for an ECHO/IMT test. One year and four years after enrollment, a sub-cohort will also be scheduled for an EBCT test.

(g) Follow-up contact schedule (frequency, type of visit/phone, in-clinic, major assessments):

Baseline visit procedures will be repeated at annual in-clinic visits. During the *follow-up* phase, participants will be contacted by telephone six months after the baseline and annual clinic visits to update contact information and assess health resource utilization and recent medical events.

(h) Primary outcome, secondary outcomes:

Outcomes regarding progression of renal disease will focus principally on reductions in GFR and level of proteinuria, as well as the occurrence of clinically relevant declines in renal function (e.g., 50% drop in GFR or ESRD). Primary outcomes regarding cardiovascular disease (CVD) will focus on clinical events indicative of ischemic heart disease, congestive heart failure, stroke, and

peripheral vascular disease, supplemented by radiographic evidence of progressive CVD (e.g., by echocardiography).

(i) Brief summary of power estimates used to justify sample size/duration, including critical assumptions (i.e., effect-size estimates, estimated event rates, or rate of change in outcome measures):

An excerpt from the CRIC Study protocol with a detailed description of power and sample size considerations is included in Appendix D. The actual power to detect specified associations will depend on the particular outcome of interest (e.g., CVD events, slope of change in GFR, etc.), the underlying rate or progression of disease, the distribution of risk factors in our study population, the alpha error we are willing to tolerate, and the proportion of our cohort members who are included in the analysis. For example, analyses including coronary calcification data, will have 1,000 of the 3,000 cohort members contributing data. For other subgroup analyses, we may have yet smaller sample sizes available. Power can be calculated for each of the types of analyses we envision, including traditional cohort analyses incorporating time to event (e.g., CVD and ESRD) analyses, followed by nested case-cohort analyses, and, finally, analyses focusing on the difference in the slope of continuous measures such as GFR.

(j) Web site:

Please refer to the CRIC Study website at **www.cristudy.org**. The web site has both features for public use and features for research study network-only use.

3. Data and Biological Sample Resources

(a) Biological samples collected in ongoing studies/research projects (specify the type of sample, e.g., blood, urine, etc., the amount—and the point in the study when samples were collected, e.g., baseline visit #1, baseline visit #2, follow-up visit #1; specify months after randomization/study entry):

No biological samples have been collected to date. Collection of these will commence with enrollment in the spring of 2003. Please see Section 2(f) above, which describes the visit schedule and plan for sample collection.

(b) Biological samples currently in storage from completed trials (grid showing sample collection time, type of sample, amount, and number of study participants the sample was collected from, in addition to physical location of where the samples are stored):

No biological samples have been collected to date. Collection of these will commence with enrollment in the spring of 2003.

(c) Brief summary of typical informed consent provisions (template informed consent form acceptable), including major variables in participant consents, if applicable (e.g., "use for other studies or not", "allow genetic studies or not"). Does consent include use of samples in other studies that are not part of the main study ?

See Appendix I for sample consent template provided to the clinical centers for local IRB review.

(d) Data collected (grid of data collection by time/clinic visit with specificity on the type of information collected, e.g., quality of life with SF-MOS 36, measurement of kidney function by GFR, serum creatinine measurement, etc.)

The anticipated study visit schedule is attached in Appendix E.

(e) Any provisions for distributing resources outside of the study? What is the sharing plan?

This plan is in development. An extensive plan for ancillary studies is in place. The CRIC Study Ancillary Studies policy is attached in Appendix F.

4. Ancillary Studies

(a) Process and contact person (name, address, phone, fax, and e mail address) for application to perform ancillary studies:

Please see the attached ancillary study policy, Appendix F.

(b) List of ancillary studies approved, completed, and ongoing (including source of funding and amount):

Please see Appendix G.

5. List of Publications and Presentations (full citations, also note manuscripts in progress):

Please see Appendix H.

*Cooperative Agreement, Contract, and Selected Investigator-Initiated NIDDK-Supported Studies

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Appendix D. Power and Sample Size

SAMPLE SIZE AND POWER CONSIDERATIONS

Overview

The actual power to detect specified associations will depend on the particular outcome of interest (e.g., CVD events, slope of change in GFR, etc.), the underlying rate or progression of disease, the distribution of risk factors in our study population, the alpha error we are willing to tolerate, and the proportion of our cohort members who are included in the analysis. For example, analyses including coronary calcification data will have 1,000 of the 3,000 cohort members contributing data. For other subgroup analyses, we may have yet smaller sample sizes available. Power can be calculated for each of the types of analyses we envision. We focus this discussion on the analyses that will have the least power to detect differences in outcomes. First, we consider traditional cohort analyses incorporating time to event (*e.g.*, CVD and ESRD) analyses, followed by nested case-cohort analyses and, finally, address analyses focusing on the difference in the slope of continuous measures such as GFR.

Time to Event Analyses

Data on the event rate of CVD in patients with CRI are available from several sources (69;71;204). Jungers et al. (69) estimated that the rate of myocardial infarction ranges from 0.62 to 2.78% per year among men, and 0.16 to 1.27%/year among women, depending on age. Consistent with these findings, others (204) reported a rate of CVD in subjects with mild CRI of 2.3%/year, where CVD included coronary heart disease, CHF, and stroke. A separate report by this same investigator (71) reported an incidence of cardiac ischemia, MI, and cardiac mortality of 3% per year among Framingham study subjects with more than trace proteinuria, and 2% per year among those with trace proteinuria. This was similar to the rate of 3.5% per year for the combined outcome of MI, stroke, or CV death in the MicroHOPE study of individuals with diabetes mellitus and either prior CVD or one additional CV risk factor. Finally, among the subset of 980 subjects in the HOPE trial with CRI (approximately one third with diabetes mellitus) and prior CVD or an additional CV risk factor, the rate of the composite CV outcome was 5.8% per year.

Data on the rate of ESRD among individuals with CRI suggest an event rate of similar magnitude to that reported for CVD. For example, in a study of benazepril (22) to slow the progression of CRI, there was a 3%/year rate of ESRD; similar to the average rate reported from the MDRD, study A.

Based on these data, we estimated the detectable hazard ratio for a range of analyses that include all or subsets of the CRI cohort, a range of exposure prevalence, a risk of outcome events in the non-exposed group of either 0.02/year or 0.04/year or 0.06/year, an alpha error

of 0.05, and 80% power (Table 10) using a log-rank test. A potential loss of follow-up of 4% per year was incorporated within the calculations. Under the assumptions of a recruitment period of 33 months, and additional follow-up time of 42 months, the detectable hazard ratios in Table 10 were computed under 80% power requirements. For the entire cohort of 3,000 subjects, using the most conservative estimate of 2% for the incidence of CVD events per year (conservative because it is the lower range reported in the literature, and because our sample will be enriched with subjects with diabetes who are at higher risk), we will be able to detect a hazard ratio of 1.65 if the prevalence of the exposure is only 10%. For a subset analysis with 1,500 subjects, relevant to the subset analyses of the diabetes-specific subgroups, we will be able to detect hazard ratios of 1.95 for an exposure with prevalence 10%, and 1.57 for exposure prevalence 50%. Finally, if we examine a subgroup with only 500 subjects, we will be able to detect hazard ratios of 2.82 for an exposure prevalence of 0.10, and 2.08 for an exposure prevalence of 0.50.

Table 10. Minimum Detectable Hazard Ratio from Proportional Hazard Analysis, Alpha error=0.05, Power=0.80; Loss-of-follow-up Rate=4%

#Subjects in Analysis	Exposure Prevalence	Length of Follow-up								
		42 months			66 months			90 months		
		Event risk/yr in non-exposed group			Event risk/yr in non-exposed group			Event risk/yr in non-exposed group		
		0.02	0.04	0.06	0.02	0.04	0.06	0.02	0.04	0.06
200	0.1	4.31	3.21	2.78	3.76	2.89	2.55	3.45	2.70	2.42
200	0.5	2.97	2.30	2.05	2.64	2.11	1.91	2.45	2.00	1.83
300	0.1	3.52	2.71	2.38	3.12	2.46	2.20	2.88	2.32	2.10
300	0.5	2.50	2.01	1.81	2.25	1.86	1.71	2.11	1.78	1.65
500	0.1	2.82	2.25	2.02	2.54	2.07	1.89	2.38	1.97	1.81
500	0.5	2.08	1.74	1.60	1.91	1.64	1.52	1.81	1.57	1.48
1,000	0.1	2.20	1.84	1.68	2.02	1.72	1.60	1.92	1.65	1.55
1,000	0.5	1.72	1.50	1.41	1.61	1.43	1.35	1.54	1.39	1.32
1,500	0.1	1.95	1.67	1.55	1.81	1.58	1.48	1.73	1.52	1.44
1,500	0.5	1.57	1.40	1.32	1.48	1.34	1.28	1.43	1.31	1.26
3,000	0.1	1.65	1.46	1.38	1.55	1.40	1.33	1.50	1.36	1.30

Extending the CRIC for an additional 2 yrs. (66 mos.) or 4 yrs. (90 mos.) beyond current plans, improves detectable risk ratios only slightly. For example, for all diabetics (N = 1,500), assuming an annual event risk of 4%, the detectable hazard ratio only improves from 1.67 to 1.52 for a risk factor with exposure prevalence = 10%, by this extension of follow-up for 4 additional years. A small gain in power with longer follow-up is related to attenuation of cohort (4% lost-to-follow-up per year).

Case-Cohort Analyses

Case-cohort analyses will be performed with subsets of our entire cohort without substantial loss of power compared to the full cohort analysis. Table 11 shows the power

for case-cohort analysis, assuming that 1,000 subjects (1/3 of the total study subjects) are in the subcohort that has additional testing. The bottom two rows show the minimum detectable hazard ratios when associations apply to the entire study cohort. Other rows apply for associations within smaller subsets of the study cohort (e.g., diabetics).

Table 11. Minimum Detectable Hazard Ratio from Case-Cohort Analysis, Alpha error=0.05, Power=0.80, Loss-of-follow-up=4% Subcohort 1/3 of Total Cohort (1000 subjects)

#Subjects in subgroup for analysis	Exposure Prevalence	Event Risk per Year in Non-exposed Group		
		0.02	0.04	0.06
200	0.1	5.10	4.02	3.64
200	0.5	3.39	2.71	2.48
300	0.1	4.09	3.28	3.00
300	0.5	2.80	2.31	2.13
500	0.1	3.20	2.64	2.42
500	0.5	2.28	1.95	1.82
1,000	0.1	2.43	2.08	1.93
1,000	0.5	1.83	1.62	1.54
1,500	0.1	2.12	1.85	1.74
1,500	0.5	1.66	1.49	1.43
3,000	0.1	1.75	1.57	1.50
3,000	0.5	1.44	1.33	1.29

These analyses are conservative because most of the laboratory measures to be analyzed in the case-cohort analyses will be continuous, whereas the formulas shown here are for binary predictor or exposure variables, which tend to yield lower power.

Analyses of Slope of Iothalamate GFR and Predicted GFR

We plan to measure iothalamate GFR values at baseline, two and four years after enrollment. We are interested in detecting the difference of slope (ml/min per 1.73m^2 per year) in GFR between exposed and unexposed subgroups within the CRIC cohort. The calculation of detectable differences in slope depends on several factors; the standard deviation of GFR measured cross-sectionally at the same point in time, the correlation of repeated measures within subjects, sample size, exposure prevalence, the number and timing of GFR measures, the alpha error, and power. We used AASK data to obtain an estimate the standard deviation of GFR of 12.9 ml/min per 1.73m^2. Also using AASK data, we estimate the correlation between repeated measurements to be 0.732.

Table 12 displays the detectable slope differences (ml/min/1.73 m^2/year) at various total sample sizes and exposure prevalences, assuming two-sided hypothesis testing at the 5% level (188). Total is the total number of subjects recruited at the beginning of the study. An anticipated rate of loss to follow-up of 4% per year is accounted for in the calculation

of the detectable slope differences assuming no replacement of lost subjects. For a proposed iothalamate-GFR-subcohort size of 1,000, an exposure prevalence of 0.1, iothalamate-GFR measures at baseline, 2, and 4 years of follow-up, we will be able to detect slope differences of at least 0.76 ml/min/ 1.73m^2 per year with 80% power.

Table 12. Detectable Iothalamate GFR Slope Differences Under Specified Parameters: Exposure Prevalence=0.1,0.5; Annual Loss-of-follow-up = 4%

Time (Years)	Total	Exposure prevalence=0.1		Exposure prevalence=0.5	
		80% power	90% power	80% power	90% power
(0, 2, 4)	1,500	0.62	0.71	0.37	0.43
(0, 2, 4)	1,000	0.76	0.88	0.45	0.53
(0, 2, 4)	800	0.85	0.98	0.51	0.59
(0, 2, 4)	600	0.98	1.13	0.59	0.68
(0, 2, 4)	500	1.07	1.24	0.64	0.74

Analysis of Slope in Coronary Calcification

A total of 1,000 subjects will undergo measurement of coronary calcium scores at one and four years of follow-up. Since there are no preliminary data to estimate the standard deviation of calcium score and correlation between repeated measurements, we examined several studies in the literature such as Goodman and Tamashiro (184), (205). We selected the median standard deviation of 605 among these studies to perform the sample size calculation using a moderate correlation of 0.5 between repeated measurements. Table 13 presents the minimum detectable slope differences at various total sample sizes and values of exposure prevalence, assuming two-sided hypothesis testing at the 5% level. Total is the total number of subjects recruited at the beginning of the study. Loss of follow-up of 4% per year is accounted for in the calculation of the detectable slope differences assuming no replacement of lost subjects. For our proposed subcohort size of 1,000, even if the prevalence of exposure is 0.1, we can detect slope difference in coronary calcium score of at least 63.270 per year with 80% power.

Table 13. Detectable Slope Difference in Coronary Calcification Under Specified Parameters; Exposure Prevalence=0.1,0.5; Annual Loss-of-follow-up = 4%

Time		Total	Exposure Prevalence=0.1		Exposure Prevalence=0.5	
			80% power	90% power	80% power	90% power
1	4	4,000	31.640	36.612	18.984	21.967
1	4	3,500	33.822	39.137	20.293	23.482
1	4	3,000	36.536	42.277	21.922	25.366
1	4	2,500	40.020	46.309	24.012	27.785
1	4	2,000	44.751	51.784	26.851	31.070
1	4	1,500	51.670	59.789	31.002	35.873
1	4	1,000	63.270	73.213	37.962	43.928
1	4	800	70.738	81.854	42.443	49.113
1	4	600	81.681	94.517	49.009	56.710
1	4	500	89.528	103.597	53.717	62.158

Appendix E. Study Visit Schedule

CRIC Visit Schedule	Pre-Screen	Screen-ing	Base Line	6 Mos.	Y 1	18 Mos.	Y 2	30 Mos.	Y 3	42 Mos.	Y 4	54 Mos.	Y 5
Type of Contact	**Phone**	**Visit**	**Visit**	**Phone**	**Visit**	**Phone**	**Visit**	**Phone**	**Visit**	**Phone**	**Visit**	**Phone**	**Visit**
Eligibility Assessment	X	X											
Informed Consent		X											
Medical Record Consent		X			X		X		X		X		X
Contact Information		X		X	X	X	X	X	X	X	X	X	X
Labs: Serum creatinine, cystatin C, glucose		X											
Demographic Information		X											
Eligibility Confirmation		X	X										
Medical History [CV, renal, health behaviors]			X		X		X		X		X		X
Genetic Sample			X		X		X		X		X		X
Labs: [CBC, metabolic panel, cholesterol, triglycerides, cystatin C, HbA1C, homocysteine, troponin I, PTH, fibrinogen, uric acid]			X		X		X		X		X		X
Urinary Assay: 24 Hour Urine [creatinine, protein, albumin, urea nitrogen]		X	X		X		X		X		X		X
AB Index & Anthropometric Measures, BIA			X		X		X		X		X		X
Toenail Clippings			X		X		X		X		X		X
ECG			X								X		
Echocardiogram					X						X		
EBT (1/3 Participants)					X						X		
I-GFR (1/3 Participants)			X				X				X		
Physical Activity Assessment			X				X				X		
Concomitant Medications			X		X		X		X		X		X
Health Care Resource Utilization			X		X		X		X		X		X
Quality of Life Questionnaire			X		X		X		X		X		X
Dietary Assessment			X				X				X		
Psychometric Testing			X		X		X		X		X		X
Cognitive Function Testing			X		X		X		X		X		X
Recent Medical History – Event information				X	X	X	X	X	X	X	X	X	X

Appendix F. DRAFT Ancillary Studies Policy

I. General Policy

To enhance the value of the CRIC Study, the Steering Committee welcomes proposals from individual investigators to carry out ancillary studies. Nevertheless, to protect the integrity of the CRIC Study, such ancillary studies must be reviewed and approved by the Primary and Ancillary Studies Committee and the Steering Committee before their inception or submission of a proposal for external funding consideration.

II. Definition of Ancillary Study

An ancillary will propose the collection of additional data not collected or analyzed as part of the routine CRIC Study data set. Ancillary studies may be submitted by the investigators within the CRIC Study or by investigators without a prior relationship to the CRIC Study. Ancillary studies require external (non-CRIC Study) funding. Examples include studies funded by investigator-initiated NIH research awards (RO1s), grants from academic institutions or private sources (e.g. private foundations, pharmaceutical companies). Any ancillary study must have sufficient funding to cover the costs incurred by the CRIC Study Clinical Centers and Laboratories (e.g., to process or ship samples), and to the Scientific and Data Coordinating Center (for tasks such as sample selection, preparing and documenting analysis files, participating in statistical analysis, and integrating the new ancillary data back into the combined CRIC Study database). There are no funds available for these purposes within the CRIC Study.

III. Requirements and Procedures for Approval of an Ancillary Study

IIIa. Overview

Participation in, and approval of an ancillary study is subject to review by the CRIC Primary and Ancillary Studies Committee, and formal approval by the CRIC Steering Committee. Under specific, selected conditions (e.g. an imminent funding deadline), the CRIC Executive Committee may serve as the proxy for the Steering Committee, although this is expected to be a relatively uncommon situation. Approval by the Steering Committee will be defined by seven of nine votes in favor of the proposal. Dissenting voters must provide the explicit reason for their dissent. Any issues of concern to dissenting voters will be shared with the applicant and opportunities for clarification provided. All sites (Clinical Centers, Scientific and Data Coordinating Center, NIH) agree to cooperate with approved ancillary studies regardless of their individual vote. An ancillary study must receive approval before a grant to support it is submitted. Investigators are encouraged to discuss potential proposals with the Chair or Co-chair of the Primary and Ancillary Studies Committee, or the Study Chair of the CRIC Study prior to submitting a concept proposal.

All ancillary study proposals must include at least one CRIC investigator as a co-investigator. Willingness to including additional CRIC investigators as co-investigators of the ancillary study is mandatory. If another site wishes to participate in the ancillary study, they should contact the proposing

investigator directly with the assistance of the Chair or Co-chair of the Primary and Ancillary Studies Committee, if needed.

III b. Requests for Ancillary Studies as Part of Training or Career Awards

The CRIC Study investigators and the NIH anticipate that the CRIC Study will be an important resource for career development and training among members of the academic community. Special consideration, therefore, will need to be given to requests for ancillary studies to be funded through training grants or career development awards through the NIH or other funding sources. As these funding mechanisms typically provide funding only for investigator effort, not additional data collection, such proposals will generally propose research questions and analyses that could be considered part of the core CRIC Study. In these cases, consideration of what analyses will be authorized could present a conflict with the interests of the CRIC investigators. Evaluation should consider the scientific gain to the CRIC study from the addition of the proposed ancillary analyses as well as the training and career development opportunities afforded to the applicant by the proposed ancillary study.

Evaluation in the case of proposals to be funded through training grants will be limited to trainees of CRIC study investigators, as the quality of the analyses will be greatly dependent on the mentor identified in the training grant. In the case of faculty career awards, evaluation of ancillary study applications will need to consider the anticipated scientific contribution of the applicant, including their ability to perform data analyses that may not be able to be performed at the SDCC without additional funding. Further, willingness to adhere to the requirements of the Publications and Presentations Committee with respect to authorship will be particularly important.

The review process will have two steps. The first step is review of the proposal concept and acceptability by the Primary and Ancillary Studies Committee. The proposal concept should be summarized in 2-4 pages.

III c. Considerations for Approval

A. The proposed study must meet requirements of the highest scientific merit.
B. Participant burden
    1. The proposed study must be acceptable to the participants (e.g. time, discomfort, privacy).
    2. The proposed study must not interfere with other parts of the main CRIC Study.
    3. The proposed study must not hamper continued participation in the main Study.
    4. The proposed study must put minimal demand on scarce CRIC Study resources such as blood samples.
C. The proposed study must require the unique characteristics of the CRIC Study cohort to accomplish its goals.

The investigators must have adequate resources to effectively complete the project, including:

1. Sufficient budget and personnel
2. Staff having the requisite expertise to meet the objectives of the project.

E. The ancillary study investigators must agree to return the complete ancillary data set back to the CRIC Study if requested by the CRIC Study Steering Committee.
F. The proposed study must not interfere with the completion of the main objectives of CRIC Study.
G. The proposed study must not adversely affect participant cooperation or compliance with CRIC Study.
H. The proposed study must not create a serious diversion of study resources (personnel, equipment or study samples) or investigator/staff time, either locally or centrally.
I. The proposed study must not jeopardize the public image of the CRIC Study.
J. Documented involvement of the CRIC investigators as part of the research team.

III d. Instructions for Preparation of Requests for Approval of an Ancillary Study

All proposed ancillary studies must be submitted to the CRIC Primary and Ancillary Studies Committee in time for circulation and subsequent review by the Steering Committee before submission to a funding agency. Studies submitted for review less than 6 weeks before a funding application deadline may not receive approval. Under specific conditions (e.g. an imminent funding deadline) the CRIC Executive Committee may serve as the proxy for the Steering Committee. The following are the elements to be included in an ancillary study proposal.

III e. Proposal Format

A written request for approval of an ancillary study should be submitted as a two to three page summary to the Primary and Ancillary Studies Committee containing the following information:

A. Identifiers:
   1. Initiating investigators, collaborators, CRIC Study co-investigator
   2. Planned starting date and project timeline
   3. Funding plans and estimated cost
B. Design and Methods
   1. Brief background and rationale
   2. Study questions or hypotheses
   3. Specific data collection methodology, including questionnaires and coding forms, if available.
C. Specific answers to the following questions
   1. What is the expected burden to participants? What are the time burdens, discomfort and expected participation rates?
   2. What CRIC Study core data and/or analyses are needed for the ancillary study?
   3. Is blood or other biologic samples (either fresh or from the CRIC Study's repository of stored samples) required? What will be the quantity of specimens needed?
   4. What collaboration with CRIC Study investigators is planned? With whom? Have the collaborating investigators approved the proposal?
   5. What, if any, follow-up is needed? Specify length of time and events to be ascertained.
   6. How many participants are required?
   7. When will data be collected? Could the ancillary study be deferred to a later exam cycle?

8. How will the ancillary study be funded? Would any additional un-reimbursed work or personnel time be expected of the CRIC Study? How will the ancillary study budget cover demands on CRIC Study personnel time and Study resources?
9. Where will the data analyses be conducted?
10. How will the confidentiality and other aspects of protection of human subjects be maintained?
11. When and in what form will a complete data set be returned to the CRIC Study?

D. Data or Specimen Requirements:
   1. Data needed from CRIC Study analysis files
   2. Specimens needed from CRIC Study repositories, specifying type and amount

E. Handling of CRIC Study Data and Specimens:
   1. Disposition of stored samples from main study and those processed by ancillary study
   2. Disposition of ancillary study data at the conclusion of the ancillary study

Approval Process

The investigator should send his/her ancillary study proposal to the Chair of the Primary and Ancillary Measures (PAM) Subcommittee who will distribute it to all members of the PAM Subcommittees along with an approval ballot. The proposal should be written in sufficient detail so that the Subcommittee can assess the study's scientific merit and potential impact on the CRIC Study. To ensure thorough scientific review, the Chair of the PAM Subcommittee may elect to seek outside expert opinion in advance of the Committee meeting. The subcommittee members will have ten days from receipt of proposal and ballot to return their completed ballot to the DCC. No response will be considered approval. Within fifteen days of receiving the proposal, the Chair of the PAM Subcommittee (or designee) will summarize the questions, as well as any objections, raised by members of the Committee in the approval ballots. The PAM Chair will then forward this summary to the applicant so that he/she may revise or withdraw his/her request. Copies of the summary will be forwarded to the Subcommittee members.

If not withdrawn, the members of the PAM Subcommittee may revisit the request in light of the applicant's response to the original summary. The Chair of the PAM Subcommittee (or designee) will prepare a statement of the Subcommittee consensus, including any remaining reservations or objections. If the ancillary study requires access to the CRIC Study patient specimens, the approval statement and all correspondence with the applicant will be forwarded to the Executive Committee. If the Executive Committee approves the release of the specimens, the proposal will be forwarded to the Steering Committee for review. If access to study specimens is not requested, the approval statement of the PAM Subcommittee and applicant correspondence will be forwarded directly to the Steering Committee. Each CRIC Steering Committee member should respond to both the Chair of the PAM Subcommittee and DCC representative within 15 days. Approval or disapproval is based on majority opinion. The investigator may only proceed with the ancillary study once it has been authorized by the CRIC Steering Committee.

Changes to Proposed Study

Once an ancillary study is approved, if a change occurs in the structure or concept of the study, such changes should be disclosed to the Primary and Ancillary Studies Committee, and the CRIC Steering Committee, for review and approval.

Proposal Budget

The investigator applying for an ancillary study must supply all additional funds needed to complete successfully the study. The Primary and Ancillary Studies Committee will be concerned with both the obvious and the hidden costs to the CRIC Study entailed by an ancillary study. Provision of funds for these expenses is essential – an ancillary study cannot begin without such fiscal support to the core study. The need for such support must be stressed in research grant applications since this support is a mandatory ingredient. Such costs include, but are not limited to:

a) Statistical and data management staff for coordinating the additional data management and analyses.
b) CRIC Study expenses involved in altering key identifying data so that subjects' confidentiality will be protected.
c) Costs for notification of alert values.
d) If work is to occur on site, rental of appropriate clinic, lab and office space
e) If subject recruitment outside of main exams is anticipated, subject coordinator to arrange subject appointments.
f) Personnel, equipment, and supplies necessary to complete the project.

Once a study concept is approved, applicants for ancillary studies must work in conjunction with the SDCC to develop a budget that adequately provides for these types of expenses at both the SDCC and Clinical Centers.

Human Subjects/Data Confidentiality

Confidentiality of CRIC participants must be guaranteed. Individually identifiable data may not be released. A signed consent must be obtained from every participant in the ancillary study, if the data collection/request is not covered in the original informed consent process for the main CRIC Study.

a) Any investigator or personnel having access to CRIC subject data should have received an orientation on the CRIC Study confidentiality policy. Key personnel of the ancillary study must be certified in the NIH OHSR or equivalent training course.
b) A copy of the IRB letter for the ancillary study is to be sent to the Scientific Project Manager at the Scientific and Data Coordinating Center. If a separate consent form is required for the ancillary study, a copy of the signed ancillary study consent form for each study participant must be included in the CRIC Study record. A data file tracking all signed ancillary consent forms must be maintained by the ancillary study and an electronic copy of that file must be delivered to the CRIC Study.

The principal investigator of an ancillary study is responsible for presenting the study to the Primary and Ancillary Studies Committee or Steering Committee as appropriate, monitoring the study to assure continuing compatibility with CRIC Study and serving as a liaison to the CRIC Steering Committee. The CRIC Steering Committee monitors the development of the ancillary studies,

receipt of funding, initiation dates, and progress. A written progress report on ancillary studies must be made periodically to the Steering Committee and the Monitoring Board.

VII. Analysis and Publication of Results of Ancillary Studies

Unless specifically arranged, all analyses will take place at the SDCC and be conducted under the supervision of its biostatistician-investigators. Under specifically approved circumstances, datasets will be released for analysis by external investigators. Ancillary studies funded as career or training awards as well as studies taking place in a subset of clinical centers may be situations in which release of data for analysis deserves special consideration. Under these circumstances, the investigator of the ancillary study will provide interim reports on analyses to the SDCC during data analysis to ensure that all study data used in analysis of ancillary study results are consistent with data in the main study database and to ensure the quality of analytical approaches. Proposals for manuscripts resulting from all ancillary studies shall be submitted for review to the Presentations and Publications Committee and require approval by the Steering Committee before establishment of a writing committee or a submission for publication or presentation. It is anticipated that principal investigators of approved ancillary studies will lead at least one scientific paper emerging from the ancillary study analyses as specified in the Publications and Presentations Policy. Each manuscript and abstract would be expected to include a CRIC investigator. The phrase "CRIC Study" should be included in the title in all scientific presentations and manuscripts and listed as a key word whenever possible. Manuscripts will also contain an appendix listing CRIC investigators deemed appropriate.

VIII. Feedback of Results of Ancillary Studies to Participants

Results of ancillary studies shall be reported to participants and/or their physicians if medically useful. Such reporting should follow standard CRIC protocol for notification of participants.

IX. Handling of CRIC Data and Specimens

At the time of distribution of CRIC specimens and/or information, the CRIC Collaborating Investigator, with help from the Coordinating Center, will make explicit arrangements with the ancillary study PI for the security of these study materials, and for their final disposition at the conclusion of the ancillary study. The safety and confidentiality of the CRIC data at the collaborating institution is the responsibility of the ancillary study PI, as is the appropriate disposition of these materials after the study has been completed. Leftover DNA and laboratory specimens are destroyed or returned, and files of CRIC data are returned or deleted, as established at the outset of the collaboration. An archival copy of the newly collected data and/or laboratory results not already held at the SDCC will be sent to the CRIC Coordinating Center at the conclusion of the data analysis and publication of the main (ancillary) study hypothesis. This transfer is the responsibility of the ancillary study CRIC collaborator(s). Once transferred back to the CRIC, these ancillary data will become part of the aggregate CRIC data. Subsequent access to these data will be governed by the CRIC Study Policy on Use of Archived Study Data.

CRIC Ancillary Study Approval Ballot

Ancillary Study Title: _____

Investigator Name: _____

Date: _____

Please check one of the following responses and include detailed explanations where appropriate. Please forward electronically your completed ballot to XXXX and Raymond Townsend, M.D., Chair of the PAM subcommittee, by XXXX. No response will be considered approval.

_____ Yes, I approve the above Ancillary Study

_____ Yes, I approve the above Ancillary Study with the following modifications:

_____ No, I do not approve the above Ancillary Study (please explain):

Subcommittee Member Name: _____

Date: _____

Appendix G. Ancillary Studies Summary

Ancillary Study Proposals Approved by the CRIC Steering Committee			
	INVESTIGATOR AND INSTITUTION	TOPIC	STATUS
1.	**Neil R. Powe, MD, MPH** The Johns Hopkins University	Chronic Kidney Disease, Diabetes and Depression	Approved by Steering Committee RO1 **Submitted** to NIH 7/1/02 RO1 **Resubmitted** 10/1/02
2.	**Cheryl A. M. Anderson, PhD, MPH** University of Pennsylvania	Nutrition Assessment In Chronic Renal Insufficiency Cohort (CRIC) Study Population	Minority Supplement to SDCC CRIC Study Award **Funded** 9/1/02
3.	**Andrew S. Levey, MD** Tufts University School of Medicine	Development and Validation of GFR Prediction Equations for Clinical Practice.	Approved by Steering Committee RO1 **Submitted** to NIH 7/1/2002
4.	**Jeffrey C. Fink, MD, MS** The Johns Hopkins University	Role of non-opioid analgesics in the progression of chronic kidney disease	Approved by Steering Committee RO1 **Submitted** to NIH 10/1/2002 RO1 to be **Resubmitted** 2/1/2003
5.	**Kevin C. Mange, MD, MSCE** University Of Pennsylvania	Molecular epidemiology of CRI	Approved by Steering Committee RO1 **Submitted** to NIH 10/1/2002
6.	**Mahboob Rahman, MD, MS** Case Western Reserve University	Ambulatory BP monitoring in chronic renal disease	Approved by Steering Committee RO1 **Submitted** to NIH 10/1/2002
7.	**Mary Leonard, MD, MSCE** University of Pennsylvania	Structural effects of renal bone disease in CRI	Approved by Steering Committee RO1 **Submitted** to NIH 10/1/2002
8.	**James P. Lash, MD & Mark A. Kraus, MD, Ph.D.** *University of Illinois*	Mentorship in the design and execution of clinical trials	Approved by Steering Committee K23 **Submitted** to NIH 10/1/2002

9.	**Bruce M. Robinson, M.D**. University of Pennsylvania	Insulin Resistance in Chronic Renal Insufficiency	Approved by Steering Committee Application **Submitted** to Baxter 10/12/2002 K23 **to be submitted** to NIH 2/1/2003
10.	**Francis Weng, M.D.**	Hypovitaminosis D in Chronic Renal Insufficiency	Approved by Steering Committee K23 **to be submitted** to NIH 2/1/2003
11.	**Vivian Fonseca, M.D.**	LDL Carbamylation and Progression of Atherosclerosis in Chronic Renal Failure	**Steering Committee approved**, expected for submission 2/1/2003
12.	**Muredach Reilly, MB** University of Pennsylvania	Genetic epidemiology of sub-clinical atherosclerosis in CRI	Approved by Steering Committee RO1 **to be Submitted** to NIH 2/1/2003
13.	**Alan S. Go, MD & Michael G. Shlipak, MD MPH** UCSF	Diagnosis of cardiac failure in patients with renal insufficiency	Approved by Steering Committee RO1 **to be Submitted** to NIH 2/1/2003
14.	**Jiang He, MD, and Paul Whelton, MD** (Tulane University)	Urinary Electrolyte Excretion and Cardiovascular Disease in CKD Patients	Steering Committee approved, **expected for submission** 6/1/2003
15.	**TBN**	Diabetic Retinopathy	In development – **Pending Steering Committee approval**, expected for submission 6/1/2003
16.	**James P. Lash, MD**	Sleep Disturbances	In development, **Pending Steering Committee approval,** expected for submission 6/1/2003

Appendix H. Publications and Presentations

Publications

Feldman, HI, Appel, LJ, Chertow, GM, Cifelli, D, Cizman, B, Daugirdas, J, Fink, JC, Franklin-Becker, ED, Go, AS, Hamm, LL, He, J, Hostetter, T, Hsu, C, Jamerson, K, Joffe, M, Kusek, JW, Landis, JR, Lash, JP, Miller, ER, Mohler, III, ER, Muntner, P, Ojo, AO, Rahman, M, Townsend, RR, Wright, JT, and The Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. The Chronic Renal Insufficiency Cohort (CRIC) Study: Design and Methods. J *Am Soc Nephrol.* (In Press)

Presentations

Feldman, HI, Landis, JR, Gaughan, C, Joffe, M, Xie, S, Greene, T, Franklin-Becker, ED, Kusek, J, Beck, G, Levey, A and the CRIC Study Group. MDRD Study Equations for Measuring Changes in GFR in Longitudinal Studies. [Poster] American Society of Nephrology, Philadelphia, PA, November, 2002.

Appendix I. CRIC Sample Informed Consent Form

SEPARATE SIGNATURE REQUIREMENTS FOR <u>OPTIONAL</u> GENETIC SAMPLE

PROCEDURE FOR GENETIC/DNA SAMPLE: You will be asked to allow genetic testing on a blood sample that will be collected and stored as part of the CRIC study. This test does not require a separate blood draw.

DNA is the part of your blood sample that holds genetic information. Your DNA sample will be stored at a central laboratory under a code number. All results of genetic testing will be stored under a code number without personal identifiers in a secure, password-protected database. The researchers who view this database will not have access to your name or identifying information. You will not be informed of any of the results of the genetic testing on your DNA. The results will not be placed in your medical record. Your blood sample will be used to prepare DNA. DNA extracted from the blood will be used to study cardio-vascular disease, kidney disease and related conditions. DNA can be removed from blood samples and stored separately for future genetic analyses. Or, to provide a larger amount of DNA from your blood for analysis in the future, we can store your blood in a way that that allows blood cells to live and grow indefinitely. This is called creating a cell line from your blood cells. The DNA samples will be kept for up to 50 years or through the end of the study.

RISKS: The kind of genetic information being analyzed in the CRIC study is not likely to have any direct effect on your health. There is the unlikely risk that if people other than the researchers got your genetic information they could misuse it. The chance of this ever happening to you is very small.

The risks of the blood draw are the same as listed in the RISKS section of the consent for participation in the study.

BENEFITS: There is no direct benefit to you for participating in the genetic part of the CRIC study. You will not be informed of any results of the genetic testing on your DNA. However, your contributions may benefit medical practice through knowledge gained.

CONFIDENTIALITY: Results of DNA testing will be kept private. DNA will be stored at a central repository under the direction of the National Institutes of Health and NIDDK with a code number by the CRIC study for future investigations. These future investigations may include medical research projects for other medical conditions. The NIDDK repository has been established to store samples from many research projects around the country in order to conduct large research studies. Your name or other information that could identify you will not appear on the DNA samples or results. Only certain study Investigators who are working directly with the genetic samples will have the master code that links your name with the code number. This master code will be kept in a secure location.

To help insure your privacy, this study operates under a Certificate of Confidentiality from the Federal Government. This certification means that researchers cannot be forced to tell people who are not

connected to this study, including courts, about your participation unless you give written consent. Conducting the study under this Certificate helps to ensure your privacy.

Researchers who plan to use your sample for future scientific study will have to request and receive all of the necessary approvals from the NIDDK and CRIC study investigators before using your sample. Samples will only be released to scientists who are qualified and prepared to conduct a research study.

ALTERNATIVES: Your alternative is not to participate in this genetic testing.

VOLUNTARY CONSENT: Your participation in the genetic testing part of this research study is voluntary. You may choose not to join in this part of the study even if you decide to participate in the CRIC study previously described in this informed consent form.

If you do decide to participate in this genetic testing, but later you change your mind, you must notify the Investigator listed on the front of this informed consent form in writing so that no additional genetic testing will be performed.

You may also decide to participate in some level of genetic testing but not another, as specified in the choices below.

CONSENT FOR GENETIC TESTING

Instructions: For each question, please **CIRCLE *"YES"*** or ***"NO"*** and write your initials and today's date in each row where indicated. Please circle either ***"YES"*** or ***"NO"*** for each of the following 4 questions.

			Initials	**Date**
1. *I give my permission to prepare DNA from my blood samples*	***YES***	***NO***	_____	_____
2 *I give my permission to create a cell line from my blood cells.*	***YES***	***NO***	_____	_____
3. *I give my permission to test my DNA for genes related to the main goals of this study: learning the causes and effects of diseases of the kidney, heart and blood vessels.*	***YES***	***NO***	_____	_____
4. *I give permission to test my DNA for genes related to other health conditions.*	***YES***	***NO***	_____	_____

SIGNATURES:

I have had the optional genetic testing section of this research study explained to me. I have read the informed consent document. I have had the chance to ask questions. They have been answered to my satisfaction.

My signature below means that I voluntarily agree to participate in the genetic testing part of the research study. I have chosen the types of testing I have agreed to. I will be given a copy of this form for my records.

Date	Signature of Participant	Printed Name
	(Or Legally Authorized Representative – note relationship to participant)	

Date	Signature of Witness	Printed Name
	(Only required if the participant can not read this consent)	

I have discussed the optional genetic testing part of the research study with the participant or his/her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed the participant of the nature of this study and its possible benefits and risks.

Date	Signature of Person Obtaining Consent	Printed Name